by G at position 139 ~~(e.g., SEQ ID NO:981)~~; or any combination thereof. These particular proteins have also been found herein to have increased resistance to proteolysis.

Please delete the following paragraph beginning at page 89, line 26 to page 89, line 31:

A modified IFNβ-1 cytokine, comprising mutations ... of the native amino acid residue(s).

Please delete the following paragraph beginning at page 90, line 1 to page 90, line 6:

A modified IFNβ-2a cytokine, comprising mutations ... of the native amino acid residue(s).

Please replace the 7th row of Table 3 on page 142 of the specification with the following amended row:

c37-39	[[147]]	G37N/P39S	147	G37N/P39T

ICF 1.28.09 **Please replace the paragraph beginning at page ~~148~~ 149, line 14 of the specification with the following amended paragraph:**

Four mutants with mutations ~~to additional~~ in addition to those selected by ~~the~~ rational mutagenesis were generated in the *E. coli* MutS strain and were detected by sequencing. The mutants were the following: E41Q/ D94G ~~SEQ.ID No. 199~~; L117V/ A139G ~~SEQ.ID No. 204~~; E41H/ Y89H/ N45D ~~SEQ.ID No. 198~~; and K121Q/ P109A/ K133Q/ G102R ~~SEQ.ID No. 204~~.

numbering is that of the mature protein (SEQ ID NO:1): L3, P4, R12, R13, M16, R22, [[K23]] R23, F27, L30, K31, R33, E41, K49, E58, K70, E78, K83, Y89, E96, E107, P109, L110, M111, E113, L117, R120, K121, R125, L128, K131, E132, K133, K134, Y135, P137, M148, R149, E159, L161, R162, K164, and E165. Each of these positions was replaced by amino acid residues, such that they are defined as compatible by the substitution matrix PAM250 while at the same time the replacement amino acids do not generate new sites for proteases.

Please replace the paragraph beginning at page 139, line 25 with the following amended paragraph:

A top and side view of IFNα-2b structure in ribbon representation (obtained from NMR structure of ~~IFNα-2b~~ IFNα-2a, PDB code 1ITF) depict residues in "space filling" defining (1) the "receptor binding region" as deduced either by "alanine scanning" data and studies by Piehler et al., *J. Biol. Chem.*, 275:40425-40433, 2000, and Roisman et al., *Proc. Natl. Acad. Sci USA*, 98:13231-13236, 2001, and (2) replacing residues (LEADs) for resistance to proteolysis.

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7.28.09 **Please replace the paragraph beginning at page ~~153~~, line 23 with the following amended paragraph:**

Antiviral activity of IFN β was determined by the capacity of the cytokine to protect [[Hela]] HeLa cells against EMC (mouse encephalomyocarditis) virus-induced cytopathic effects. The day before, [[Hela]] HeLa cells (2 x 10^5 cells/ml) were seeded in flat-bottomed 96-well plates containing 100 µl/well of Dulbecco's MEM-GlutamaxI-sodium pyruvate medium supplemented with 5% SVF and 0.2% of gentamicin. Cells were growth at 37°C in an atmosphere of 5% CO_2 for ~~24 hours~~

~~Two-fold~~ 24 hours. Two fold serial dilutions of interferon samples were made with MEM complete media into 96-Deep-Well plates with final concentration ranging from 1600 to 0.6 pg/ml. The medium was aspirated from each well and 100 µl of interferon dilutions were added to [[Hela]] HeLa cells. Each interferon sample dilution was assessed in triplicate. The two last rows of the plates were filled with 100 µl of medium without interferon dilution samples in order to serve as controls for cells with and without virus.

Please replace the paragraph beginning at page 153, line 5 with the following amended paragraph:

After 72 hours of growth, 20 µl of Cell titer 96 Aqueous one solution reagent (Promega) was added to each well and incubated 1H30 at 37°C in an atmosphere of 5% CO_2.

AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph beginning at page 4, line 18 with the following amended paragraph:

Provided herein are methods for generating modified cytokines based on structural homology (3D scanning). These methods are based on the spatial and topological structure; they are not based on their underlying sequences of amino acid residues. The methods are used for identification of target sites for mutagenesis, particularly in families of target proteins. The targets are identified through comparison of patterns of protein backbone folding between and among structurally related proteins. The methods are ~~exemplifed~~ exemplified herein for cytokines. Families of the modified cytokines also are provided herein.

Please replace the paragraph beginning at page 6, line 18 with the following amended paragraph:

The modified cytokines have use as therapeutics. Each cytokine has improved biological and or therapeutic activity, compared to the know activity of the unmodified cytokine. Accordingly, uses of the cytokines for treatment of cytokine-mediated diseases and diseases for which immunotherapy is employed are provided. Methods of treatment using the modified cytokines for diseases also are provided. Each cytokine has a known therapeutic use, and such use is contemplated herein. ~~Cyokines~~ Cytokines provided herein have improved properties, such as increased bioavailability, improved stability, particularly *in vivo*, and/or greater efficacy.

wsl 7.28.09 **Please replace the paragraph beginning at page 8, line 27 with the following amended paragraph:**

Figure 6(G) provides graphs indicating the *in vitro* potency for antiviral activity, for IFNα-2b variants produced in bacteria. The vertical axis indicates the level of antiviral activity and the horizontal axis indicates concentration of the variants at which each level of activity is achieved. The activity for the variants (~~continous~~ continuous line with gray circles) was compared to that of the wild-type IFNα-2b (black triangles with dashed lines). The potency for each variant was calculated from the graphs as the concentration at the inflection point of the respective curves. Figure 6(T) shows the value of potency obtained for each variant tested compared to the wild type IFNα.

provided herein that possess increased resistance to proteolysis result in a decrease in the frequency of injections needed to maintain a sufficient drug level in serum, thus leading to, for example: *i*) higher comfort and acceptance by patients, *ii*) lower doses necessary to achieve comparable biological effects, and *iii*) as a consequence of (*ii*), likely attenuation of any secondary effects.

lmf 7.28.09 **Please replace the paragraph on page 96, line 28, to page 97, line 17, with the following amended paragraph:**

Two methodologies were used to address the improvements described above: (a) 2D-scanning methods were used to identify ~~aminoacid~~ amino acid changes that lead to improvement in protease resistance and to improvement in conformational stability, and (b) 3D-scanning, which employs structural homology methods ~~methods~~ also were used to identify ~~aminoaci~~ amino acid changes that lead to improvement in protease resistance. The 2D-scanning and 3D-scanning methods each were used to identify the amino acid changes on IFNβ that lead to an increase in stability when challenged either with proteases, human blood lysate or human serum. Increasing protein stability to proteases, human blood lysate or human serum is contemplated herein to provide a longer *in vivo* half-life for the particular protein molecules, and thus a reduction in the frequency of necessary injections into patients. The biological activities that have been measured for the IFNβ molecules are *i*) their capacity to inhibit virus replication when added to permissive cells previously infected with the appropriate virus, and *ii*) their capacity to stimulate cell proliferation when added to the appropriate cells. Prior to the measurement of biological activity, IFNβ molecules were challenged with proteases, human blood lysate or human serum during different incubation times. The biological activity measured, corresponds then to the residual biological activity following exposure to the proteolytic mixtures.